REMARKS

Claims 68, 70-72, 75-80, 82-83, and 85-114 are presently pending in the case. Claims 97-107 and 112-114 are withdrawn. Claims 1-67, 69, 73-74, 81, and 84 stand cancelled. Claim 110 is newly cancelled. Claims 68 and 70 are hereby amended to incorporate the limitations of claim 110. Claims 83, and 108 are hereby amended to correct obvious typographical errors as the claims were previously dependent on cancelled claims and to correct the typographical error in claim 83. Claim 93 is hereby amended to include additional dosages which are fully supported in the specification, for example, on page 20, line 18. Claims 115-122 have been added. The claims are fully supported by the specification, for example claims 115-118 are supported in Table 1 of Example 1, and claims 119-122 are supported on page 1, lines 14-17 and page 12, lines 19-32. Upon entry of the amendment, claims 68, 70-72, 75-80, 82-83, 85-96, 108-109, 111, and 115-122 will be pending and under examination.

As a preliminary matter, Applicant thanks the Examiner and her Supervisor for their time and courtesy during the telephonic interview on September 10, 2008. No agreements were reached.

Withdrawal of rejections

Referring now to the Office Action, Applicant thanks the Examiner for the withdrawal of the rejection of the claims for obviousness in view of Penkler, sometimes in view of Sallman.

Double patenting rejection

Claims 68, 70-72, 75-80, 82-83, 85-86, 91-92, 95-96, and 108-111 stand rejected on the grounds of nonstatutory obviousnesss-type double patenting over claims 1-3, 8-17, 22-29 and 34-37 of US Patent No. 6,713,089.

The Office Action alleges that claim 1 of the '089 patent covers the claim limitations of solubility, particle size, pKa of the active compound, contacting an aqueous media, particle size of the particulate composition, release rate of the active

composition using a specific dissolution method, and the composition comprising a pharmaceutically acceptable excipient. The Office Action further suggests that the difference between claim 1 of the '089 patent and the instant claims is the use of the term "dissolves" in the instant claims as opposed to the term "releases" in claim 1 of the '089 patent.

Applicant submits that the claims of the instant application are not obvious in view of the claims of the '089 patent

However, without agreeing with the Examiner and solely to progress prosecution of the application, a terminal disclaimer is filed herewith. The rejection is overcome.

Rejection under 35 U.S.C. §103

Claims 68, 70-72, 75-80, 82-83, 85-86, 91-92, 95-96, and 108-111 are rejected under 35 U.S.C. §103(a) over Nemoto et al (JP 03-240729, hereinafter Nemoto). Applicant notes that the reference was referred to as Masami in the parent application.

The Office Action asserts that Nemoto teaches all of the elements of the invention. The Office Action points to the results of Nemoto from solubility tests in artificial gastric juice to demonstrate that the compositions made by the methods of Nemoto have the same properties as the compositions of the instant claims.

Applicant respectfully disagrees. The issue of obviousness in chemical cases has been reviewed by the Courts in view of the recent KSR decision.

> "While the KSR Court rejected a rigid application of the . . . TSM test in an obviousness inquiry, the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination."
>
> "When there is a design need or market pressure to solve a problem and there is a finite number of ***identified, predictable solutions***, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S. Ct. at 1732. * * * That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of

> compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound." *Takeda Chemical Industries Ltd. v. Alphapharm Pty.* 492 F.3d 1350 (Fed. Cir. 2007) [emphasis added]

The *KSR* decision does not abrogate the need for some suggestion in the reference or in the art to modify a particular reference in a particular manner. As noted in the TC1600 teaching examples for determining obviousness in view of KSR, "The Examiner is still required to provide a reasoned statement of the rejection grounded in the Graham inquiries. He or she must articulate a reason or rationale to support the obviousness rejection." [slide 2, emphasis in original] "Examiners must account for all claim limitations in their rejections by explaining how each limitation is disclosed or rendered obvious by the reference(s) applied." [slide 5, emphasis in original]

During the telephonic interview, Examiner Woodward asserted that one of skill in the art would recognize particle size as a "result effective variable." To make a rejection for obviousness, a particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) Applicant submits that no reference has been provided by the Examiner to demonstrate that one of skill in the art would recognize particle size as a "result effective variable". Applicant notes that Nemoto teaches the compositions that do not granulate well cannot be used. Applicant submits that "the recognized result" of using claimed particulate sizes was that tablets could not be properly formed. One of skill in the art would not be motivated to "optimize" a composition by working in a range that is accepted to be outside of the functional ranges of the parameter.

Applicant requests that the Examiner provide a reference ***related to formulation of pharmaceutical compositions*** for tableting or filling of capsules demonstrating that one of skill in the art would expect that the use of granules of the claimed size would result in a pharmaceutical composition appropriate for tableting. That is a reference

that would demonstrate that one of skill in the art would know that modification of the granule size in the claimed range could be a "result effective variable." Applicant notes that in the 10 formulations taught by Nemoto, there is no teaching or suggestion to modify the method of making granules for the preparation of tablets or capsules. MPEP 2143.01 (III) states:

> The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.,* 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007)("If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."). [emphasis in the original]

The claimed invention is not a "predictable variation" of the teachings of Nemoto. The claimed invention is a variation not expected to be an operable composition for the desired purpose. Therefore, it cannot be obvious.

Applicant provides herewith selected pages from Remmington's *Pharmaceutical Sciences*, 16th Edition (1980) (hereinafter *Remmington's*) which discusses the process of wet granulation and tableting and provides some example formulations made by the wet granulation method. On page 1544 of *Remmington's*, there is a table that provides a conversion between sieve size and opening size in mm and μm. Methods of tablet preparation are discussed beginning in column 2 on page 1560. The last line in the first column of page 1561 (underlined) states "The wet granulation is forced through a 6- or 8-mesh screen." The table indicates that an 8 mesh screen has openings of 2.38 mm. No value is given for a 6 mesh screen, but a 4 mesh screen has openings of 4.76 mm. The first paragraph on page 1563 (bracketed) states:

> After drying, the granulation is reduced in particle size by passing it through a smaller mesh screen. Following dry screening, the granule size tends to be more uniform. For dry granulations, the screen size to be selected depends on the diameter of the punch. The following sizes are suggested.

Tablets up to 3/16-in. diam., use 20-mesh

Tablets 7/32 in. to 5/16 in., use 16-mesh

Tablets 11/32 in. to 13/32 in., use 14-mesh

Tablets 7/16 in. and larger, use 12-mesh

Applicant notes that the same information ins provided in the 21st Edition of *Remmington's* (page 898, copyright 2006, copy enclosed).

Mesh sizes provided in the Table on page 1544 are 10-mesh with a sieve opening of 2.00 mm and 20 with a sieve opening of 0.84 mm. The claims require that the particles of the composition of the invention either have a mean particle size of at most 0.250 mm, or that at least 50% pass through a 180 mm sieve, which would correspond to about an 80 mesh sieve per the table in *Remmington's*. Moreover, the indication that mesh size should be selected based on the size tablets to be prepared demonstrates that one of skill in the art did not, and still does not, condiser granulation particle size to be a "result effective variable."

Pages 1572 and 1573 of *Remmington's* provide some example formulations prepared by the wet granulation method. Applicant has underlined the size mesh indicated for screening the dried granules in each of the formulations. Suggested screen sizes range from 12-mesh to 20-mesh. There is no suggestion to use a smaller mesh size, moreover, *Remmington's* cautions against the generation of excess fines in the preparation of compositions for tableting.

In the middle of the first column on page 1563, applicant has bracketed discussion regarding the importance of maintaining granule size during the application of lubricant by gentle mixing of the composition. Specifically, *Remmington's* states:

> Gentle action is desired to maintain the uniform granule size resulting from the dry-granulation step. It has been claimed that too much fine powder is not desirable because fine powder may not feed into the die evenly; consequently, variations in weight and density result. Fine powders, commonly designated as "fines," also blow out around the upper punch and down past the lower punch, making it necessary to clean the machine

> frequently. Air trapped in the tablets by the fine powder causes them to split apart after ejection from the machine.

As noted below, Nemoto teaches the undesirability of certain formulations as they result in tablets that crack or do not tablet well due to poor granulation (i.e., are smaller than the particle size taught by Nemoto).

Applicant submits that there would be no motivation to modify the methods of Nemoto as they do not provide a problem to be solved. The Advisory Action disagrees with this assertion noting that "Nemoto states that the "rapid action of anti-inflammatory drugs is remarkably improved" (Page 4), thereby showing the problem to be solved." As noted above in *Takeda* (citation omitted), "When there is a design need or a market pressure ***to solve a problem***.... a person of ordinary skill has a good reason to pursue the known options." Applicant asserts that Nemoto solves the problem that was noted by Nemoto in the prior art. Nemoto "***remarkably improved***" the properties of the agents. No problem remains.

During the telephonic interview, Examiner Woodward noted that this reading was a very narrow reading of the reference. Applicant disagrees. Applicant asserts that the reading takes the teachings of the reference as a whole, as required when making an obviousness rejection. When all capsule preparations are completely dissolved in 5 minutes (see Table 4, page 10) and one tablet preparation is completely dissolved in 5 minutes, as compared to 10% for the control, and three are completely dissolved in 10 minutes, as compared to 20% for the control, one would consider that no problem remained to be solved. The MPEP notes that the results of the modification of the reference needs to be obvious and there must be some motivation to modify the cited art to make an obviousness rejection. Specifically, MPEP 2143.01 (IV) states:

> A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). "'[R]ejections on obviousness cannot be sustained by mere conclusory

> statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). [emphasis in original]

There can be no "rational underpinning" to modify the teachings of a reference that provides a composition that has all of the desired characteristic, as in Nemoto. In *Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick* (464 F.3d 1356, 1368, 80 USPQ2d 1641, 1651 (Fed. Cir. 2006)), it was noted that "Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the 'improvement' is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient." There is no room for "improvement" of Nemoto. It is already 100% efficient at the earliest time point tested. It cannot be made faster or more efficient.

Table 3 on page 9 and Table 4 on page 10 of Nemoto demonstrate that the methods of Nemoto provide any of a number of compositions that have more than satisfactory dissolution rates in simulated gastric juice using the method provided. Therefore, no design need or market pressure is present. Moreover, the teachings of Nemoto demonstrate variations in the specific components of the compositions, but ***the methods of making the tablets are the same throughout all of the examples in the reference***. Nemoto neither teaches nor suggests that varying the method for tablet preparation could alter dissolution properties, or how one might alter methods of tablet preparation to alter dissolution properties. Therefore, based on the teachings of Nemoto one would not be motivated to vary the methods for preparation of tablets.

In regard to the shortcomings of Nemoto, the Office Action expressly acknowledges that Nemoto does not provide "testing the dissolution of the composition by employing 0.07N HCl as dissolution media." However, the position is taken that it would have been obvious to test the compositions of Nemoto in 0.07N HCl and "produce the instant invention" (page 7).

Applicant submits that the testing method to determine dissolution rate is not an element of the invention, but instead a method to characterize compositions made by the method of the invention. The testing method allows for comparison of the dissolution properties of various compositions to determine if compositions have the desired properties and fall within the scope of the claims. Upon testing, the compositions of Nemoto were found to not meet the dissolution property requirement of the claim. As the composition of Nemoto does not meet the dissolution requirement of the claim, Nemoto cannot render the instant claim obvious.

Moreover, the Nemoto reference was cited in the prosecution of the parent application as noted above. A Declaration was filed by one of the inventors Poul Bertelsen (copy enclosed) in which the dissolution of a composition made based on the teachings of Nemoto was tested using the method required in the claims of the instant invention. The results are provided in Appendix A of the Declaration. After 1 hour, the composition made according to the teachings of Nemoto with a 1:5 ratio of oxicam to antiacid was found to release only 37.8% in 0.07N HCl. Therefore, the amount released after 20 minutes must have been less than 50% as required by the instant claims. The composition with a 1:5 ratio of oxicam to antacid when tested by Nemoto dissolved 73.5% in 20 minutes. This demonstrate that the results from the testing method of Nemoto do not predict the results from the testing method required by the claims. This deficiency in the teachings of Nemoto to make a composition that has the claimed properties is not discussed in the Advisory Action.

The Declaration of Poul Bertelsen further discusses other aspects of the invention in the currently pending dependent claims that further differentiate the instant invention from the Nemoto reference.

Paragraphs 5-8 of the Bertelsen Declaration discuss the differences between the particulate composition recited in the claimed methods (e.g., in currently amended claims 68 and 70) and the methods of Nemoto. Nemoto teaches the preparation of "an oral solid preparation" (page 2, first full paragraph). This preparation requires granulation, which includes preparation of aggregates to make larger particles more

suitable for compression into tablets. Specifically, the Mesh 20 used by Nemoto (last sentence on page 5) corresponds to a particle size of about 800 μM.

A goal of the granulation step of Nemoto was "the production of granules having good fluidity" (third full paragraph, page 3). Formation of granules is necessary for the formation of tablets and for filling capsules. Nemoto frequently comments about the inappropriateness of certain combinations of antacid and oxicams as they prevent the formulation of good granules and have undesirable properties that prevent tableting. Not only must the composition of Nemoto have good dissolution properties, it also must be appropriate for the formation of tablets or filling capsules. This is accomplished by Nemeto by using granulation. For example, Nemoto states:

> However, if more than 20 parts by weight are blended, hardness decreases thereby preventing suitable tablets from being obtained, and if more than 15 parts by weight are blended, the tablets are subject to cracking and chipping during coating. (last paragraph, page 2)
>
> If more than 40 parts by weight are blended, however, granulation becomes difficult, thereby preventing the production of granules having good fluidity... if more than 20 parts by weight are blended, the ease of forming of the granules becomes poor causing the surface of the granules to chip during coating (third paragraph, page 3)

Therefore, an essential aspect of the Nemoto reference is the ability to form granules, and subsequently form tablets or fill capsules with them, ***in addition*** to being able to provide a composition with good dissolution properties. Nemoto teaches against compositions that prevent good granulation. If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Nemeto repeatedly teaches that granulation is an essential aspect of the invention to prepare granules with "good fluidity" that can optionally be formed into tablets. Any modification that does not include the formation of granules with "good fluidity" would render the reference unsatisfactory for its intended purpose. Therefore, there can be no suggestion or motivation to modify the reference to exclude the formation of granules.

The Leiberman reference, provided with the Declaration, demonstrates that those skilled in the art considered that enlarging particles into aggregates (i.e., granulation) should be performed to "***render the material free flowing***." This is because

> Most powders cannot be compressed directly into tablets because (a) they lack the proper characteristics of binding or bonding together into a compact entity and (b) they do not ordinarily possess the lubricating and ***disintegrating properties*** required for tableting. For these reasons, drugs must first be pretreated, either alone or in combination with a filler, to form granules that lend themselves to tableting. This process is known as granulation.
>
> Granulation is any process of size enlargement whereby small particles are gathered together into ***larger, permanent aggregates*** [22] to render them into a free-flowing state similar to sand. (first full paragraphs, page 148, emphasis added)

Therefore, it is clear from the teachings of Leiberman that smaller is not always better. Granulation, the generation of larger particles, is necessary to provide powders with desirable properties for manufacturing solid dosage forms. Instead, it is asserted in the Office Action that "A person having ordinary skill in the art at the time the invention was made would know that smaller granules or particles would lead to a faster dissolution rate by virtue of the increased surface area of the granular or particulate composition." Applicant respectfully disagrees and points to Leiberman to support their position.

> As noted in the MPEP (2144.03)"
>
> While "official notice" may be relied on, these circumstances ***should be rare when an application is under final rejection*** or action under 37 CFR 1.113. Official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known. As noted by the court in *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970), the notice of facts beyond the record which may be taken by the examiner must be "***capable of such instant and unquestionable demonstration as to defy dispute***" (citing *In re Knapp Monarch Co.,* 296 F.2d 230, 132 USPQ 6 (CCPA 1961)). [emphasis added]

Applicant asserts that the reliance on common knowledge is inappropriate in a final rejection, and moreover, the "common knowledge" asserted was contrary to a reference in the case. Applicant requests that the Examiner provide a reference ***relating to manufacturing of pharmaceutical compositions*** for oral administration demonstrating that in the size range of particles claimed, mean particle size of about 250 micrometers, that one of skill in the art would know that smaller granules would allow production of oral compositions with a faster dissolution rate. In the absence of support for such a statement, withdrawal of the rejection is respectfully requested. Applicant notes that the size of the granules in the claims does not refer to a pure pharmaceutically active substance, but instead to the combination of the active substance with the alkaline substance.

Examples 15-17 and Tables 8-10 of the instant application demonstrate that the use of particles that pass through a 180 μM sieve or have a mean particle size of at the most 250 μM, which is far smaller than is either taught or suggested by Nemoto (or *Remmington's*), results in a final composition with a high dissolution rate. Applicant submits that based on the teachings of Nemoto, one would not be motivated to make the instantly claimed compositions having a small particle size. The rejection of claim 110 (the limitations of which are now incorporated into claims 68 and 70) set forth in the Office Action does not consider the size limitation included in the claim (page 9). Instead the Office Action states that the use of the dissolution test of the claims would have been obvious in view of the dissolution test of Nemoto.

Claims 87-90 and 93-94 are rejected for alleged obviousness over Nemoto further in view of Penkler (US 5,854,226, hereinafter the '226 patent).

The '226 patent does not remedy the deficiencies of Nemoto. The documents, even in combination, fail to teach or suggest the feature of the invention wherein the particles of the particulate composition used in the manufacture of the composition pass through a 180 μM sieve or have a mean particle size of at most 250 μM. As discussed above, the Nemoto requires the formation of large granules for the preparation of tablet compositions. The '226 patent provides no suggestion which would cause one skilled

in the art to modify the teachings of Nemoto to use a particulate composition used in the manufacture of the composition pass through a 180 μM sieve or have a mean particle size of at most 250 μM, as claimed presently. The rejection is therefore properly withdrawn.

There is no suggestion or motivation, either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the cited reference(s) to make the claimed invention, nor is there a reasonable expectation of success.

The newly added claims are novel and non-obvious. Claims 115 to 118 are drawn to compositions based on the compositions provided in Example 1. Applicant provides herewith a catalog page from Sigma Chemical Company demonstrating that the trade name Avicel® listed in the Example refers to microcrystalline cellulose as claimed. No new matter is added.

Claims 119 to 122 recite specific properties of the granules. Claims 119 and 120 recite that the composition has sufficient mechanical strength to enable the composition to be coated using traditional coating equipment. Nemoto repeated states that granules must be sufficiently large to allow for tableting; therefore, one would not expect that granules having the claimed properties would be appropriate for the method of the invention. Moreover, the limitation provides an effective lower limit to the size of the particles of the composition. Claims 121 and 122 define the mechanical strength of the claimed tablets. Method to test crushing strength are well known to those in the art.

FEES

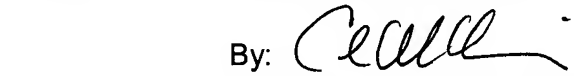
Applicant hereby authorizes the Commissioner to charge Deposit Account No. 04-1105 the fee for a Terminal Disclaimer, a Request for Continued Examination, and a three month Extension of Time for Response citing Docket No. 55682CON(71432). It is believed that no further fee is due with this response. However, if a further fee is due,

the Commissioner is hereby authorized to charge any fee or credit any overpayment to the Deposit Account noted referencing the docket number of the instant case.

In view of the above amendments and remarks, Applicant believes the pending application is in condition for allowance.

Dated: September 11, 2008

Respectfully submitted,

By: 

Colleen J. McKiernan, Ph.D.
Registration No.: 48,570
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617)517-5555
Attorneys/Agents For Applicant
Customer No.: 21874